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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,904	12/02/2003	Kei Roger Aoki	16952CON1CIP3 (BOT)	4172

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EXAMINER	
GUPTA, ANISH	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	10/726,904	AOKI ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants amendment, filed September 26, 2006 is acknowledged. Claims 1 and 5 were amended. Claims 1-5 are pending in this application.

Priority Under 35 U.S.C. 119

2. Applicants request that priority to parent application 08/173,996 be granted since the parent application provide ample support for the claimed invention. Applicants state that the "parent application fully describes the effective amount of the botulinum toxin free of complex protein (i.e. pure botulinum toxin) to treat strabismus." Applicants refer to pinpoint citations in the parent application as support for their contention. The parent application, it is asserted, discloses neurotoxic component of a botulinum toxin having molecular weight of about 150kDa "which can be useful in a method of present invention" and "conventional techniques are known in for culturing and purifying a botulinum toxin." Furthermore, with regards to dosage Applicants state that "determining the effective amount for a pharmaceutical agent (which would be the pure botulinum toxin in the present case) in a particular medical condition (which would be strabismus in the present case) is well within the ordinary skill in the art."

Applicants arguments have been fully considered but have not been found persuasive and the priority to parent application 08/173,996 is hereby denied.

The MPEP states:

> The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the prior application and in the later-filed application must be **sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112.** See Transco Prods., Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). The prior-filed application must disclose the common named inventor's invention claimed in the later-

> filed application in the manner provided by the first paragraph of 35 U.S.C. 112. See 37 CFR 1.78(a)(1). Accordingly, the disclosure of the prior-filed application must provide adequate support and enablement for the claimed subject matter of the later-filed application in compliance with the requirements of 35 U.S.C. 112, first paragraph."

See MPEP 201.11. Thus, the parent application must comply with both written description and enablement under 35 U.S.C. 112 First Paragraph.

Lack of Written Description

Applicants state that the parent application describes "botulinum toxin free of complex protein (i.e. pure botulinum toxin)." However, in reviewing the application, the phrase "botulinum toxin free of complex protein" or variations thereof to treat medical conditions is not present. The specification is limited to the use of "botulinum toxin type A" rather than pure botulinum toxin or complex free botulinum toxin. The disclosure of the components on page 3 of the parent application does not provide written description since the disclosure does not teach nor imply that only the 150kda component is utilized. Note that on page 4, the disclosure states that botulinum toxin type A is generally found under the trade name "DYSPORT" or "BOTOX." These forms were identified by Applicants, in the response dated 1-12-05, as complex proteins rather than pure forms of botulinum toxin. Further, there is a distinction between botulinum toxin type and pure toxin or toxin free of botulinum toxin complex protein. This distinction does not exist in the parent application and thus one cannot conclude that the parent application provides written description for the claimed invention.

Lack of Enablement

The parent application also lacks an enabling disclosure for the use of imply pure toxin or toxin free of botulinum toxin complex protein. In response to the office action dated, 9-26-06, Applicants stated:

> "**At the time of the filing of the present application, one of ordinary skill would not consider the teachings of the Tse reference regarding the use of purified botulinum toxin to be relevant to clinical treatment, such as the treatment of cervical dystonia in humans.** For example, in 1992, Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings, Specifically, Schantz et al. states:
>
> > Most recent information concerning the structure and pharmacology of botulinum toxin has been obtained with purified neurotoxins, but it is unlikely that these will be used in clinical settings. The toxin complexes are much more stable than neurotoxin and can be diluted and formulated with retention of toxicity. Pure neurotoxins can be kept for several weeks to months in solution in the cold but are inactivated on dilution, formulation, and drying.
>
> Schantz et al., Microbiological Reviews, Mar 1992, p. 80-99, 89, second column, emphasis added, Exhibit 2. Since it was believed at the time of filing the present application that purified botulinum toxin would not be effective for clinical use, one of ordinary skill would not be impelled to combine the teachings of the Tse reference (use of purified botulinum toxin in non-clinical settings, i.e., rat experiments) with the teachings of the Balkan/Han references (use of complexed botulinum toxin in clinical setting for treating strabismus in humans)."

Applicants parent Application was filed one year and eight months after the publication of Schantz reference. However, Applicants specification neither disclosed nor implied that pure toxin was clinically ineffective, as recited by the state of the prior art at time. The specification did not disclose methods that one of ordinary skill in the art could utilize to render the pure toxin clinically effective. Given the state of the art as recited by Schantz, such information was **necessary and critical** to allow one of ordinary skill in the art to use pure toxin in a clinical setting. Without such guidance, one would be burdened with undue experimentation to practice the claimed invention. For the dosage, Applicants have stated that determining the effective amount for a pharmaceutical agent (which would be the pure botulinum toxin in the present case) in a particular medical condition (which would be strabismus in the present case) is well within the ordinary skill in the art. However,

given the teaching of Schantz, it is unclear how one would go about determining the effective amount. The parent application does not provide any guidance in this manner. Thus, since the parent application does not provide adequate support and enablement for the claimed subject matter of the later-filed application in compliance with the requirements of 35 U.S.C. 112, first paragraph, the priority is denied for 08/173,996.

3. All of the rejections made in the previous office action and not cited herein are hereby withdrawn.

4. The terminal disclaimer filed on 9-26-06 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 10/443, 593 and 6,841,156 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balkan et al. or Han et al. in view of Tse et al. and Aoki et al. (US 6,113,915) for the reasons set forth in the previous office action and the reasons set forth below.

6. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balkan et al. or Han et al. in view of Aoki et al. (US 6,113,915) and Aoki et al. (20010018415) for the reasons set forth in the previous office action and the reasons set forth below.

The claims are drawn to a method of treating strabismus using therapeutically effective amount of neurotoxin component of the botulinum toxin free of botulinum toxin protein.

Forth both rejections, Applicants raise similar points and these have been addressed below.

Applicants argue that human muscles are different than rat muscles. Applicants state that given the teachings of Jankovic et al, which state that rodent studies must be considered inconclusive with respect to predicting relative potency of various types of BTX, one would not be motivated to combine the teachings of Anderson et al. [which teaches human treatment] with Tse [which teaches administration of the toxin to rats].

Second point asserted by Applicants is that the Tse et al. teaches the administration of botulinum toxin paralyzes the muscle. In treating strabismus, one would not paralyze the muscle. "Since the Tse reference teaches the use of botulinum toxin to paralyze a muscle, one of ordinary skill in the art would not rely on such a reference."

Thirdly, Applicants contend that that it is been understood in the art that purified botulinum toxin is clinically ineffective. Applicants make reference to Schantz et al. who teaches that botulinum toxin (150Kd) is so labile that it would not be used in clinical settings. Applicants state that Schantz et al. "was fully aware that purified botulinum toxin had been tested in rats. . .Nevertheless, the Schantz reference asserts that use of purified botulinum toxin would be clinically ineffective on page 89."

Fourthly, Applicants state that Balkan/Han et al. reference have a different purpose than that of Tse reference. Tse reference utilizes the botulinum toxin for probes and vaccine purposes. The use of botulinum toxin as a drug for treating strabismus in humans is very different from the use of botulinum toxin as an antigen or a probe, and the practice of the two methods may be entirely incompatible with each other.

Fifth, the Aoki reference teaches away from the administration of present invention by teaching that purified botulinum toxin would diffuse more quickly to adjacent muscles, and thus purified toxins should not be used to treat strabismus. In "Strabismus conditions, very specific muscles are spasmodic, and only those specific muscles need to be treated with botulinum toxin. It is not desirable to that the administered botulinum toxin diffuse to adjacent muscles that need to remain untreated."

Finally Applicants state that Tse's toxin is "about 140kDa, comprising the fist polypeptide of 99kDa and second polypeptide of about 55kDa." The instant application, on the other hand, teaches a toxin "about 150 kDa comprising a short polypeptide chain of about 50kDa and long polypeptide chain about 100kDa." As a result, the two toxins are not the same. "[T]he Office Action has not provided any evidence that the two neurotoxin are the same. As such, Applicant's position that the data regarding use of 140 kDa in mouse cannot be extrapolated to human remains

unchallenged." Applicants also make virtually identical arguments with regards to the general belief that purified botulinum toxin is clinically ineffective and the teachings of the references have a different purpose than that of Tse reference. All of these arguments were addressed in the previous office actions are again reiterated. Applicants also state that one would not desire highly diffusing neurotoxin to diffuse to non targeted muscles. If a physician desires the neurotoxin to be at a certain region, then he/she would simply inject the neurotoxin into that region, for example making multiple injections along the length of the muscle.

Applicants arguments have been fully considered but have not been found persuasive.

First, the propriety of the use of the expression "about" in claims to permit "of some tolerance" is established by long practice in the Patent Office. See W.L. Gore & Associates, Inc. v. Garlock, Inc., 82 U.S.P.Q. (BNA) 303, 306 (Fed. Cir. 1983) and Ex Parte King, 82 U.S.P.Q. (BNA) 450, 451 (Pat. & Trademark Office Bd. App. 1948). The term "about" allows for some tolerance in the ranges disclosed. In In re Ayers, the Federal Circuit held that "at least about 10%" was anticipated by a reference that disclosed "about 8%" because the term "about" allowed for some tolerance. In re Ayers, 154 F.2d 182, 185 (Fed. Cir. 1946). Similarly, in Johnson and Johnson v. W.L. Gore & Associates, Inc., the Court allowed for "about 1.2" to be inclusive of 1.0. See Johnson and Johnson,436 F.Supp. 704, 728-729 (Fed. Cir. 1977). Although about has never been confined to specific percentage of variability, the Johnson and Johnson decision at least implies that 16% variability is permissible when "about" is used (1.0/1.2 = ~16.6% variability). Thus, the term about implicitly discloses some variability even though the specification may not literally cite this variability.

Here, both the instant specification and the prior art use the word "about" in defining the molecular weight. Given the tolerance allowed by Courts, one can reasonably conclude that both

the prior art toxin and the botulinum toxin disclosed in the instant application are the same. Furthermore, both the prior art and the instant application teach a toxin obtained form Clostridium botulinum and have the same activity in inhibition of acetylcholine release (see page 493 and 494 of Tse). Further, both toxin have a short polypeptide and long polypeptide. Given the source and the activity are the same in both the Applicants disclosure and Tse et al. and both have a long and short polypeptide one can reasonably conclude that the pure botulinum toxin taught by Tse et al. is the same as the claimed invention. If Applicants truly believe that the toxins are different, then Applicants are requested to provide evidence that clearly establishes that they are different. This evidence should be more than reliance on the molecular weight taught in the prior art. Depending upon the methods utilize, such as SDS gel, one can attain different molecular estimates for the same compound.

With respect to the rat studies and clinical efficiency of botulinum toxin, the reference of Kohl et al. addresses the concerns raised with respect to rat muscles. Kohl et al. Teaches the administration of botulinum toxin NT-201, a highly purified botulinum toxin that consists of pure neurotoxin. The results showed that that the paralytic effect of appears to be faster with NT-201 based on 20% CMAP decline. The maximum effect of this toxin was comparable to the complexed neurotoxin (see page 165). Note that the subjects used were human male volunteers. Thus, unlike Applicants contentions, the effects observed in mouse model of Tse et al. were reflective in Kohl et al. Note that this reference was cited in Hunt (US2003/0118598), which has the same Assignment as the instant application, as the basis to conclude that pure botulinum toxin can be formulated into pharmaceutical formulations for human use. "[P]ure botulinum toxin has been used in humans. see e.g. Kohl A., et al., Comparison of the effect of botulinum toxin A Botox (R)) with the highly-purified neurotoxin (NT201) in the extensor digitorum brevis muscle test, *Mov Disord* 2000;15(Suppl

3):165. Hence, a pharmaceutical composition can be prepared using a pure botulinum toxin." (see page 4, paragraph 043 of US2003/0118598).

Applicants argue that the Tse et al. teach that botulinum toxin for the paralyze the muscle which is counterintuitive to practice the claimed invention. Page 1-2 of Applicants specification states, with regards to treating strabismus and other similar disorders, that "[t]he toxin [Botulinum toxin] binds rapidly and strongly to presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. This results in a local paralysis and hence relaxation of the muscle afflicted by spasm." Thus, as much as Applicant would profess that paralysis is counterintuitive, their specification would indicate otherwise. Achieving paralysis is the mechanism by which the neuromuscular disorder such as strabismus is treated.

With regards to different purpose of the references, Tse was cited to show that pure botulinum toxin specifically and characteristically inhibited stimulated and spontaneous release of actetylcholine at the vertebrate neuromuscular junction. The reference states that neurotoxin free of Haemagglutinin, when injected into the hind leg muscle of a rat, produced local paralysis within 24 hours (see page 494). Note that toxin complexes inhibit the release of acetylcholne resulting in local paralysis of the muscle (see page 1-2 of the instant specification). Thus, the teaching relied upon in Tse are pertinent and in the same field as Applicants invention, namely that the reference teaches the inhibition of acetylcholine release. The paralytic effect of the pure neurotoxin is also reflected in Kohl et al.

Finally, with respect to Aoki et al., Applicants state that only specific muscles need to be treated with botulinum toxin. The point of Aoki's teaching is that, after administration at the spot of treatment, the toxin diffuses to the muscle to be treated more rapidly than complexed botulinum

toxin. While the physician can inject along the muscle length, it is not necessary since the toxin can diffuse through the muscle. One would want the toxin to diffuse rapidly, away form the site of intramuscular injection, so as to treat and denervate the entire improperly functioning muscle. This would not only achieve better treatment of the disorder, but also rapid treatment of the disorder. Note that this **assumption is reflected in Kohl et al. which states that the paralytic effect was faster with the pure neurotoxin in the muscle to be treated.**

Thus, the rejection maintained.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (571) 272-0562. The fax phone number of this group is (571)-273-8300.

12/11/08
ANISH GUPTA
PRIMARY EXAMINER